## REMARKS

These remarks are in response to the Office Action dated April 24, 2007. Applicants have canceled claims 61-64 and 66-69. Claims 65, 70, 72, 74, 76, 79, and 80 have been amended. New claims 82 and 83 have been added. New claim 82 incorporates the subject matter of canceled claim 61. Support for new claim 82 can be found throughout the specification as filed. For example, support for the recitation of "glyceryl behenate comprising about 10-36 weight percent of the formulation " in new claim 82 can be found at page 5, line 19, of the specification as filed. Support for the recitation of "hydroxypropyl methylcellulose comprising about 13-18 weight percent of the formulation and dispersed within the matrix" can be found at page 8 in Examples 1 and 3, and at page 9 in Examples 4 and 5. Additional support can be found at page 6, lines 1-4 of the specification as filed. Support for the recitation of "clarithromycin, or derivative thereof, comprising at least about 42 weight percent of the formulation and dispersed within the matrix" in new claim 82 can be found at page 8 in Examples 1 and 3, and at page 9 in Examples 4 and 5. Support for the recitation of "acid resistant coating" and "HPMC-phthalate" in claims 78 and 79, respectively, can be found at page 7, first paragraph of the specification as filed. Support for the amendments to claim 80 is equivalent to the support previously recited for new claim 82.

No new matter is believed to have been introduced. Claims 65 and 70-83 are pending and at issue. Applicants request reconsideration of the pending claims.

## INFORMAL MATTERS

Applicants wish to thank Examiner Landau for the helpful discussion with Applicants representatives on July 17th, 2007.

## I. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claim 79 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants traverse this rejection as it may apply to the amended claim. Claim 79 has been amended to recite an acid resistant coating comprising "HPMC-phthalate." In view of the amendment to the claim, Applicants request withdrawal of this rejection.

## II. REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claim 79 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants traverse this rejection and note that claim 79 has been amended to recite an acid resistant coating comprising "HPMC-phthalate." In view of the amendment to the claim, Applicants request withdrawal of this rejection.

## III. REJECTION UNDER 35 U.S.C. §102(b)

***Yajima***

Claims 61-63, 65-66, 68, 72, and 76-77 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Yajima et al. (US Patent No. 5,707,646). This rejection is moot with regard to canceled claims 61-63 and 66-68. Applicants traverse this rejection as it may apply to the amended claims and new claim 82.

New claim 82 incorporates the subject matter of canceled claim 61. Claim 82 recites a matrix comprising "a) glyceryl behenate comprising about 10-36 weight percent of the formulation; b) hydroxypropyl methylcellulose comprising about 13-18 weight percent of the formulation and dispersed within the matrix; and c) clarithromycin, or derivative thereof, comprising at least about 42 weight percent of the formulation and dispersed within the matrix." Applicants submit that the recitation of these specific components in the claimed pharmaceutical formulation eliminates Yajima as a viable anticipatory reference because the cited reference fails to recite any type of matrix that includes such components in the amounts specified in claim 82.

Accordingly, Applicants request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

***Briskin***

Claims 61-68, 76-78, and 80-81 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by or Briskin et al. (WO 95/22319). This rejection is moot

with regard to canceled claims 61-64 and 67-68. Applicants traverse this rejection as it may apply to the amended claims and new claim 82.

New claim 82 incorporates the subject matter of canceled claim 61. Claim 82 recites a matrix comprising "a) glyceryl behenate comprising about 10-36 weight percent of the formulation; b) hydroxypropyl methylcellulose comprising about 13-18 weight percent of the formulation and dispersed within the matrix; and c) clarithromycin, or derivative thereof, comprising at least about 42 weight percent of the formulation and dispersed within the matrix." Applicants submit that the recitation of these specific components in the claimed pharmaceutical formulation eliminates Briskin as a viable anticipatory reference because the cited reference fails to recite any type of matrix that includes such components in the amounts specified in claim 82.

Accordingly, Applicants request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

## IV. REJECTION UNDER 35 U.S.C. §103

***Briskin in view of Gibson***

Claims 69 and 72-73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Briskin et al. (WO 95/22319) in view of Gibson et al. (U.S. Patent No. 5,811,120). This rejection is moot with regard to canceled claim 69. Applicants traverse this rejection and will now address any issues that may be raised by the pending rejections with regard to claims 72-73 which now depend from new claim 82.

The present claims are drawn to pharmaceutical formulations, and methods of producing such formulations, that include a) glyceryl behenate comprising about 10-36 weight percent of the formulation; b) hydroxypropyl methylcellulose comprising about 13-18 weight percent of the formulation and dispersed within the matrix; and c) clarithromycin, or derivative thereof, comprising at least about 42 weight percent of the formulation and dispersed within the matrix. Applicants were the first to discover that these components could be combined to form a matrix that sustains the release of clarithromycin over a 24 hour period of time with a high degree of reproducibility (see e.g., instant specification as filed, bottom of page 4, bridging to page 5). The

instant specification teaches a matrix that releases clarithromycin through the combined modalities of glyceryl behenate disintegration and the formation of viscous microenvironments by hydroxypropyl methylcellulose (see e.g., instant specification as filed, bottom of page 5, bridging to page 6).

Briskin et al. describes a formulation that includes the components clarithromycin, hydroxypropyl cellulose, and glyceryl behenate (see Table 1, part 1b). It is clear from the specification of the cited reference that Briskin fails to appreciate the significance of forming a matrix with these components, or any combination thereof, in order to facilitate the controlled release of clarithromycin over an extended period of time. While the cited reference recites various hydrophilic polymers that can be included in a pharmaceutical formulation, Briskin fails to disclose any matrix that utilizes hydroxypropyl methylcellulose comprising about 13-18 weight percent of the formulation and dispersed within the matrix to facilitate the controlled release of clarithromycin over a period of 24 hours in conjunction with glyceryl behenate comprising about 10-36 weight percent of the formulation.

Gibson et al. has been cited as allegedly teaching conventional hydrophilic binders. Applicants acknowledge that this secondary reference provides general information about hydrophilic binders. However, Gibson fails to remedy the deficiencies of Briskin because Gibson does not suggest a matrix formulation utilizing glyceryl behenate and hydroxypropyl methylcellulose in the amounts specified in new claim 82 for the controlled-release of clarithromycin.

In the instant application, the Applicants succeeded in designing and manufacturing a pharmaceutical formulation for the extended release of clarithromycin. It could be argued that Applicants merely pursued options known to the pharmaceutical industry for producing a formulation that controls the release of an antibiotic in a living system. The Supreme Court recently addressed the issue of obviousness in KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007). The KSR Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." KSR, 127 S. Ct. at 1732. In such circumstances, "the fact that

a combination was obvious to try might show that it was obvious under § 103." Id. Applicants submit that such is not the case here.

Rather than identify predictable solutions for achieving a pharmaceutical formulation that provides extended release of an antibiotic, the prior art disclosed a broad selection of compounds any one of which could have been selected as a component in the manufacture of a pharmaceutical formulation. Further, these components can be mixed together in any number of different combinations giving rise to a myriad of formulation permutations. Finally, the amount of each component can be varied, further increasing the number of formulations that can be produced from a finite number of compounds. Applicants note that the choice of compounds to be combined, the manner in which they are combined, and the amount of each compound present in the combination, impacts the release characteristics of a pharmaceutical formulation. Applicants submit that the subject matter of new claim 82 fails to present the type of situation contemplated by the KSR Court when it stated that an invention may be deemed obvious if it was "obvious to try." New claim 82 recites specific components in specific amounts which were not "obvious to try" in the manufacture of a formulation suitable for the extended release of clarithromycin.

Further, while the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, 127 S. Ct. at 1731. Applicants submit that in cases involving new pharmaceutical formulations, it remains necessary to identify some reason that would have led the skilled artisan to combine known pharmaceutical formulation components in a particular manner, and in particular amounts, to establish prima facie obviousness of a new pharmaceutical formulation. Here, the primary reference of Briskin selected glyceryl behenate as a "preferred extrusion aid" (see page 7, line 22, of WO 95/22319) because it exhibits certain properties that prevent the destruction of extrusion screens used in the manufacture of pharmaceutical formulations. Briskin also selected hydroxymethylcellulose (HMC) as a hydrophilic binder. Significantly, Briskin fails to describe how an extrusion aid in combination with a hydrophilic binder could be

combined to modulate the release of an antibiotic from a pharmaceutical formulation. With specific regard to the subject matter encompassed by new claim 82, Briskin fails to describe the properties associated with glyceryl behenate that would have directed one of ordinary skill in the art to combine it with 13-18 weight percent HMC (or 13-18 weight percent HPMC) in order to form a matrix suitable for extended release of an antibiotic. Accordingly, nothing in the prior art suggests combining the specific components set forth in new claim 82 in a manner that achieves the claimed extended release formulation. More specifically, nothing in the prior art provides a reasonable expectation that combining glyceryl behenate and hydroxypropyl methylcellulose in the amounts specified in claim 82 would result in a matrix useful for the controlled release of clarithromycin.

In view of the amendments to the claims and new claim 82, and in light of the above discussion, Applicants request that this rejection under 35 U.S.C. 103(a) be withdrawn.

***Briskin in view of Gibson in further view of Evenstad***

Claims 70-71 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Briskin et al. (WO 95/22319) in view of Gibson et al. (U.S. Patent No. 5,811,120) further in view of Evenstad et al (U.S. Patent No. 5,126,145). Applicants traverse this rejection and will now address any issues that may be raised by the pending rejections with regard to claims 70-71 which now depend from new claim 82.

The arguments set forth above as related to ***Briskin in view of Gibson*** are herein incorporated in their entirety. Evenstad et al. fails to remedy the deficiencies of Gibson and/or Briskin. Evenstad merely provides information related to high viscosity hydrophilic binders and fails to provide any information that combining glyceryl behenate and hydroxypropyl methylcellulose in the amounts specified in claim 82 would result in a matrix useful for the controlled release of clarithromycin.

In view of the amendments to the claims and new claim 82, and in light of the above discussion, Applicants request that this rejection under 35 U.S.C. 103(a) be withdrawn.

***Briskin in view of Curatolo***

Claims 74-75 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Briskin et al. (WO 95/22319) in view of Curatolo et al. (U.S. Patent No. 5,605,889). Applicants traverse this rejection and will now address any issues that may be raised by the pending rejections with regard to claims 74-75 which now depend from new claim 82.

The arguments set forth above as related to ***Briskin in view of Gibson*** are herein incorporated in their entirety. Curatolo et al. fails to remedy the deficiencies of Gibson. Curatolo merely provides information related to buffers useful in pharmaceutical formulations. However, the cited reference fails to provide any information that combining glyceryl behenate and hydroxypropyl methylcellulose in the amounts specified in claim 82 would result in a matrix useful for the controlled release of clarithromycin.

In view of the amendments to the claims and new claim 82, and in light of the above discussion, Applicants request that this rejection under 35 U.S.C. 103(a) be withdrawn.

***Briskin in view of Khan***

Claim 79 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Briskin et al. (WO 95/22319) in view of Khan et al. (U.S. Patent No. 5,656,296). Applicants traverse this rejection and will now address any issues that may be raised by the pending rejections with regard to claim 79 which now depends from new claim 82.

The arguments set forth above as related to ***Briskin in view of Gibson*** are herein incorporated in their entirety. Khan et al. fails to remedy the deficiencies of Gibson. Khan merely provides general information related to polymeric coatings useful in pharmaceutical formulations. However, the cited reference fails to provide any information that combining glyceryl behenate and hydroxypropyl methylcellulose in the amounts specified in claim 82 would result in a matrix useful for the controlled release of clarithromycin.

In view of the amendments to the claims and new claim 82, and in light of the above discussion, Applicants request that this rejection under 35 U.S.C. 103(a) be withdrawn.

## V. CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 65 and 70-83 clearly and patentably define the invention. Applicants request that the Examiner reconsider and withdraw the various grounds for rejection set forth in the Office Action.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' representative can be reached at (858) 509-7318. No fees are believed due in the filing of this response. However, should any fees be required, the Commissioner is authorized to charge deficiencies or credit any overpayment to Deposit Account No. 02-4800.

Respectfully submitted,

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